Controlling Immune Memory Generated by Antibody Dynamics

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Abstract— Immune memory of antigens is formed as a limit behavior of antibody dynamics inspired by one-dimensional chaotic systems. Associativity of immune-memory mechanism can be investigated on the basis of dynamics determined by affinity index of antibody chains. The proposed model provides some control strategy based on the OGY method to steer immune-memory formation which is non-associative to associative memory formation which is shown by some stable periodic orbit.

Keywords: chaotic dynamical system, associative memory, antibody dynamics

1. Introduction

Immune memory is one of the major feature of immune systems, particularly, for secondary and cross reactive immune responses. Short-living memory cells which form some immune networks is an accepted model for immune memory [1]. Immune memory mechanism can be explained through Jerne’s immune network theory by regarding these as complex dynamical systems [2]. On the other hand, rather than a centralized architecture, immune memory belongs to a class of sparse and distributed associative memory [3]. Based on the above considerations, we are looking forward to building a mathematical model of immune memory mechanism which can describe such paradigm of short-lived memory cells with network dynamics.

Our idea is the following. First the traditional idiotypic immune networks (IINs) are too complicated to define network dynamics. Therefore we simplify such IINs to some network structure, namely, antibody chains. We then analyze the network dynamics of antibody chains. Morita has proposed non-monotonic dynamics for associative memory [4]. It introduced the autocorrelation matrix for such dynamics. We are inspired by such statistical dynamics for antibody chain, namely, discrete chaotic dynamical system defined by logistic function. In details, the memory format of the corresponding antigen can be defined as limiting behavior of such network dynamics. One advantage of antibody chains is its simplicity to define the network dynamics rather than population dynamics. Namely, the state transitions generated by such antibody dynamics is more suitable for population dynamics from immune memory viewpoints.

Another challenge for network dynamics of antibody chain is as follows. Is antibody dynamics inspired by logistic function a reasonable model of antigenic memory? One aspect of this question is the dynamics of cross-reactive immune response, namely, the mechanism of associative memory. In this research, such associativity can be characterized by the affinity index, which defines the degree of connection for the corresponding antibody chain. The latter can be the bifurcation parameter of the logistic function. One advantage of this model is the ability of controlling non-associative immune memory by way of perturbation structure of antibody chain successively. Moreover, such controlling technique of successive perturbations is proposed by Ott, Grebogi and York [5], or the OGY method.

The major goal of this research is to control the forming of non-associative immune memory based on antibody dynamics. There are two aspects for the latter: (1) associative memory based on chaotic immunodynamics inspired by [6][4]; (2) controlling the non-associative memory based on the OGY method [5]. One contribution of such approach is to establish the method of controlling immune memory inspired by chaotic dynamics. This research is a continued work for [7] and also inspired by Abbattista et al. [8].

2. Research Background

2.1 Immune Memory

While a specific antigen invades human body, the immune system will respond by producing some antibodies which can eliminate this invaded antigen. The typical pattern of such immune responses can be illustrated by Figure 1(a) and Figure 1(b); it has three phases, namely, first immune response, second immune response and the cross-reactive response. For the first invaded antigen $Ag$, the immune systems will produce large amount of the antibody $Ab_1$ which binds to $Ag$. Therefore the amount of antigen clones for $Ag$ will be reduced rapidly after they had reached the population peak. Simultaneously, the amount of $Ab_1$ is also declined to some constant value; we say this immune system is turned into the memory state. For the second phase, the same antigen $Ag$ invades and the remaining antibody $Ab_1$ will take less time than that of first immune response to reach the population peak. Therefore this antigen cannot proliferate immediately as it did at the first phase. This is the reason why we seldom get sick at this stage. On the other hand, if an antigen $Ag'$ which is very similar to $Ag$ invades, then the same antibody $Ab$ will also proliferate soon and eliminate $Ag'$ clones. The second and the third stages are all related to immune memory mechanism to recall the stored
information of $Ag$. We will analyze the state transitions of the invaded antigen patterns between each phase based on network structure of immune systems, in particular the idiotypic immune networks and antibody chains. We are particularly interested in the third stage which shows an associative memory mechanism for the immune response to similar antigens. The first antibody $Ab_1$ binding to $Ag$ in the immune response process is determined by the clonal selection mechanism of immune systems. $Ab_1$ secreted by some activated B-cell is the one with the highest affinity among those candidates of antibodies which are generated by hypermutation.

Immune system will react rapidly to the same or similar, even mutated antigens which had invaded the same human body before. This phenomenon implies that immune system can "memorize" associatively the formations of previously invaded antigens. One major evidence for such immune memory mechanism is that it is strongly affected by the concentration of soluble antibodies in the blood. Therefore some variables related to the immune memory might be correlated to the antibody concentration from the aspect of computational biology.

Immune memory mechanism is not fully understood so far. According to Smith et al. [3], at the end of an immune response, when the antigen clones are cleared, the B cell concentration decreases, leaving a persistent population of memory cells. The newer viewpoint of memory cells is that they are not lived longer than virgin cells; their life cycles depend on the persistence of antigens [9]. Besides memory cell mechanism, researches related to immune network theory imply the immune memory mechanism is formed by cyclic idiotypic immune networks (CIINs) than specific memory cells [10]. According to vaccinations, immune systems can react immediately to antigens which are similar to previously invaded ones. However, such theory is mainly dealt with the diversity of antibodies for antigenic recognitions by affinity matching. It is not sufficient to explain how memory recalls are activated for similar antigenic invasions. Therefore, for such associative memory mechanism of immune systems, it is worth of considering the immune network theory.

### 2.2 Antibody Chain

Idiotypic network theory implies that immune systems will emulate the presence of antigens even after they are eliminated [3]. The epitope of antibody molecule is called an "idiotope". An epitope of antigen $Ag$ is recognized by the antibody molecule $Ab_1$ and by the receptor molecule on the lymphocyte of $LU_1$. The antibody $Ab_1$ and the receptor of $LU_1$ have the idiotope which is recognized by antibody $Ab_2$ and the receptor on the lymphocyte of $LU_2$. Continuously, we reach an antibody $Ab_N$, while the antibody $Ab_1$ and the receptor on the lymphocyte of $LU_1$ also recognize idiotopes on antibody $Ab_N$. $Ab_N$ constitutes an internal image of the antigen $Ag$. Immune network is formed by interactions between lymphocyte interactions. These $LU_i$ form an closed loop, namely, closed idiotypic immune network (CIIN).

![Antibody Chain Diagram](image)

**Fig. 2: Antibody Chain**

The advantage of this simplified network, namely, antibody chain, is the following. The immune response, in
particular, immune memory, can be exploited by state transitions determined by such simplified networks. There are two stable states for idiotic immune network; for the first state, the antibody \( Ab_1 \) is not produced. For the second stable state, \( Ab_1 \) is produced and antigen may or may not be completely eliminated \([11]\). The memory of such antigen is thus established. Network models of immune responses described by dynamical systems can be referred to \([12]\)[13][14].

Given \( \lambda \) a positive integer. The relationship "\( Ab_k \) recognizes \( Ab_i \)" denoted by \( Ab_i \rightarrow \lambda Ab_k \), is defined if \( Ab_i \) and \( Ab_k \) are \( \lambda \)-complementary match; namely, there are \( \lambda \) different digits between \( Ab_i \) and \( Ab_k \). Frequently we simply write \( Ab_i \rightarrow Ab_k \) by omitting \( \lambda \) if the latter is known and fixed. For simplicity, it is reasonable that we consider antibodies from both network dynamics perspective. Certain immune network models can be contributed to this antibody dynamics such as the one proposed in \([10]\). The antibody chain, written as \( AC = \{ Ab_1, Ab_2, \cdots Ab_N \} \) is defined as follows. (1) \( Ab_i \in LU_i \), for all \( i = 1, 2, \cdots N \); (2) the idiotype of \( Ab_i \) can be recognized by the partatope of \( Ab_{i+1} \), namely, \( Ab_i \rightarrow Ab_{i+1} \), for all \( i = 1, 2, \cdots N - 1 \); (3) \( Ab_N \rightarrow Ab_1 \).

2.3 One-dimensional Chaotic System

One-dimensional chaotic systems have shown many applications in highly nonlinear systems which are sensitive dependent on initial conditions. One the best-known one-dimensional chaotic systems is the logistic function which is defined by

\[
F(x, \alpha) = \alpha \cdot x(1 - x) \tag{1}
\]

where \( \alpha \in [0, 4] \) is the bifurcation parameter of \( (1) \). Such parameter is the major character for dramatic change of system behavior. \( (1) \) also generates a one-dimensional discrete dynamical system defined as follows.

\[
x_{n+1} = F(x_n, \alpha) = \alpha \cdot x_n(1 - x_n) \tag{2}
\]

Fig. 3 is the bifurcation diagram of \( (2) \). It shows that the values of fixed points for \( (2) \) for varied \( \alpha \in [0, 4] \). While \( 1 < \alpha < 3 \), the dynamics has two fixed points, one is 0, the other is \( x = \frac{\alpha - 1}{\alpha} \). As \( \alpha \) increases, periodic orbits with periodicity 2 appears. As \( \alpha \) increases, periodic orbits with higher periodicities appear. As \( \alpha > 3.65 \), \( (2) \) shows chaotic behavior (Fig. 3).

Definition 1: Consider the discrete dynamical system \( x_{n+1} = F(x_n) \). The Lyapunov exponent of \( x_0 \) is defined by \( \lambda(x_0) = \lim_{n \to \infty} \frac{1}{n} \sum_{i=0}^{n-1} \ln |F'(x_i)| \), if the limit exists. If \( \lambda(x_0) > 0 \), then the dynamics of \( (2) \) with an initial condition \( x_0 \) is chaotic.

3. Results

Major results in this paper include the modeling of dynamics of immune memory mechanism from one-dimensional dynamical system \( (2) \). This immune memory mechanism can explain the associativity property by the chaotic property of \( (2) \).

3.1 Mathematical model of Immune Memory Mechanism

We establish a mathematical model of the immune memory mechanism. First is the definition of the immune memory function as follows.

Definition 2: The immune memory forming function \( f : \mathbb{R} \to \mathbb{R} \) is a real-valued continuous function defined on \( \mathbb{R} \) with the following condition. There exists some nonempty set \( E \subset \mathbb{R} \) such that \( \lim_{k \to \infty} f^k(x) \) exists for all \( x \in E \).

According to immune memory forming function, we can define immune memory format for antigens. The format of each antigen is the binary vector of length \( n \). Each antigen can be defined by some rational number \( x \in [0, 1] \) with finitely many digits.

Definition 3: Fixed \( k \) a positive integer. Given an immune memory forming function \( f \), the \( k \)-level immune memory of antigen \( Ag \) is defined by \( f^k(Ag) \). The immune memory of \( Ag \) is defined by \( \lim_{k \to \infty} f^k(Ag) \), if the latter exists.

Remark 1: If \( F \) is a logistic function, then \( f_\alpha(x) = F(x, \alpha) \) is an immune memory function, for \( \alpha \in (0, 1] \).

3.2 Network Dynamics of Antibody Chains

We propose a network dynamics \( F \) of antibody chains inspired by the logistic function \( (1) \). Such dynamics of state transitions can generate immune memory of any given antigen. The idea of this model is as follows. Some character of the antibody chain \( AC \) can influence the forming of
immune memory. If $AC$ has strong affinity for adjacent antibodies, it will incur strong associative memory for antigens "similar" to previously invaded antigen $Ag$. Therefore, we will describe such character at first. We first define the affinity between two molecules.

**Definition 4:** Let $n$ be the length of molecules $X$ and $Y$. The affinity between $X$ and $Y$, $\gamma(X,Y)$, is defined by $1 - \frac{d(X,Y)}{n}$, where $d$ is the Hamming distance.

Now we can define the affinity index of any given antibody chain. For an antigen $Ag$, we also assume that there exists an antibody chain $AC = \{Ab_i\}_{i=1}^N$ such that it is a CIIN. Such $AC$ can be characterized by affinity index which describes the degree of aggregation for $AC$.

**Definition 5:** The affinity index $L_{AC}$ induced by the antibody chain $AC$ is defined by

$$L_{AC} = 4 \cdot (1 - \frac{1}{N-1} \sum_{i=1}^{N-1} \gamma(Ab_{i+1}, Ab_i))$$

Therefore $L_{AC}$ is a real number in $[0,4]$. Given an antigen $Ag^T$ (column vector), we transform $Ag^T$ to a real number $x(0) = \sum_{i=1}^{n} Ag_i 2^{-i}$ between 0 and 1, where $Ag_i$ is the $i$-th component of $Ag$. For example, if $Ag = "11001"$, then $x(0) = 2^{-1} + 2^{-2} + 2^{-5} = 0.78125$.

Affinity index represents the degree of connection for the corresponding antibody chain. The smaller the index, the more associative the immune memory. Based on the affinity index, the network dynamics $F$ derived by $L_{AC}$ is the following.

$$x(n+1) = F(x(n), L_{AC}) = L_{AC} \cdot x(n)(1 - x(n))$$

$n = 0, 1, 2, \cdots$

### 3.3 Memory formed by Antibody Chains

The network dynamics $f$ generated by antibody chains activated by some antigens can generate memory formats of invaded antigens. It is similar to the dynamics of attractor networks originally proposed by [15]. Let $S$ be the set of all binary molecule formats with finite lengths. The network dynamics $F$ defined on $S$ generates antigenic format of $Ag$ by $\lim_{k \to \infty} f^k(Ag)$. If $f^k(Ag) \to s^1$, for some $s^1 \in S$, then $f$ generates an attractor dynamics (as $s^1$ is exactly an attractor of $F$), $s^1$ is also called a memory format of antigen $Ag$ (Figure 4). The domain of attraction of $s^1$, $A(s^1)$, is defined as $\{s \in S : F^k(s) \to s^1\}$. The associative memory of antigens can be defined by stable fixed points of such network dynamics.

For an immune network $AC$ activated by antigen $Ag$ with network dynamics $F$, if there exists a binary molecule format $s^1$ which is an attractor of $f$, then we say the immune network $AC$ can memorize $Ag$, if some antigen $Ag'$ is fallen into the domain of attraction of $s^1$, then $Ag'$ can invoke proliferation of the same antibody ($Ab_i$) immediately.

**Definition 6:** Let $\gamma(\cdot, \cdot)$ represents the affinity between two binary molecule formats. An immune network $AC = \{Ab_i\}_{i=1}^N$ activated by antigen $Ag$ is equipped with associative memory, if there exists some $\delta > 0$, such that whenever a new antigen $Ag'$ with $\gamma(Ag, Ag') > \delta$ implies that $Ag' \to \lambda Ab_1$.

According to this definition, if a new or mutated antigen $Ag'$ which is very similar to the previous invaded antigen $Ag$ invades, then the antibody $Ab_1$ which binds $Ag$ can also bind $Ag'$. Therefore $A'_g$ invokes cross-reactive immune response.

The network dynamics (3)-(4) may induce attractors such as stable fixed points or stable periodic orbits or even strange attractors. These attractors represent memory formats for different antigens. Memory formats are exactly some molecule attributes with dimension $n$, if attractors of (3)-(4) are stable equilibrium states. As for periodic orbit, memory format is composed by $l$ binary molecule formats, where $l$ is the periodicity of such orbit. For example, $l = 2$ represents 2-periodic orbit.

Given an antigen $Ag$ with activated antibody chain $AC = \{Ab_i\}_{i=1}^N$ with dynamics (4), then the memory format of $Ag$ is defined by the limit of $Ag$ by $F$, namely, $\lim_{k \to \infty} F^k(Ag)$, where $F$ is the network dynamics (4), see Figure 4.

Once the same or a similar" antigen to $Ag$, say $Ag'$, invades the immune system again, the memory recall process of the immune systems will be activated by comparing the $F^k(Ag')$ with $S^1$, the memory format of $Ag$. According to system dynamics, such similar antigens are elements of domain of attraction of the dynamics $f$, namely $Ag \in A(s^1)$. Suppose the same antigen $Ag$ invades the immune systems again, then $f^k(Ag)$ will immediately converges to $s^1$. On the other hand, if some similar antigen $Ag'$ invades, the
network dynamics $F^k(Ag')$ converges to $s^i$, if $Ag' \in A(s^i)$. Therefore, the domain of attraction of antigen memory format is the major criterion whether similar or mutated antigens will activate the original antibody $Ab_1$ and the same antibody chain $AC$. In this way, the dynamics of antibody chains is the key for cross-reactive immune responses which show the associative memory mechanism for the immune systems.

**Proposition 1:** Let $L^− \subset [0, 1]$ be the region of negative Lyaponov exponents of (2). Then the immune memory of an antigen $x_0$ exists, if $(\alpha, x_0) \in L^−$.

### 3.4 Controlling Associativity of Immune Memory Forming

We propose the method of controlling associativity of immune memory forming based on the OGY method. Given $(\lambda, x_0) \in L^+$. By given successive perturbations $\Delta\alpha_n$ such that the dynamics $x_{n+1} = F(x_n, \alpha + \Delta\alpha_n)$ is equal to either $(p, q)$. The latter is some stable periodic orbit. According to OGY method, $\Delta\alpha_n$ can be derived as follows.

$$\Delta\alpha_n = \alpha_0\frac{2[p - 1][x_n - p]}{p[1 - p]} \quad (5)$$

### 3.5 Simulations

We simulate memory forming process via network dynamics (3)-(4). In this way, we can analyze memory formats of mutated antigens $Ag'$ which are similar to the previously invaded and memorized antigens $Ag$ with only a few different attributes ($m$ is the number of mutated attributes). We give a complete list of parameters as (Table 1) with $\text{iterno} = 100$, $n = 30$ and $m = 5$ for every simulation. Memory formats can be represented as real number between 0 and 1.

Table 1: Parameters for Immune Networks

<table>
<thead>
<tr>
<th>Para.</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>$L_{AC}$</td>
<td>Affinity Index of Antibody Body $AC$</td>
</tr>
<tr>
<td>$\lambda$</td>
<td>Affinity Threshold</td>
</tr>
<tr>
<td>$m$</td>
<td>Number of mutated attributes from $Ag$</td>
</tr>
<tr>
<td>$\text{iterno}$</td>
<td>Numbers of Iterations</td>
</tr>
<tr>
<td>$\alpha$</td>
<td>bifurcation parameter for logistic function</td>
</tr>
<tr>
<td>$n$</td>
<td>Length of $Ag, Ab$</td>
</tr>
<tr>
<td>$N$</td>
<td>Length of antibody chain $AC$</td>
</tr>
</tbody>
</table>

#### 3.5.1 Simulation One: $3 < L_{AC} < 3.6$.

According to varied simulations, we observe that $AC$ is difficult to form if affinity threshold $\lambda \geq 0.7$. Therefore we will simulate the memory format for $\lambda \geq 0.7$ by assigning $L_{AC}$ values directly to (4) without generating antibody chains.

Fig 5 shows the memory format for $Ag$ is a stable periodic orbit 0.56, 0.76 with periodicity equal to 2. $L_{AC} = 3.1026$. As for the memory format of mutated antigen $Ag'$, Fig. 6 illustrates a better view that two memory formats are identical (after 30 iterations). The mutated antigen $Ag'$ induces a cross-reactive immune response activated by original antibody chain, as its memory format is also convergent to that of $Ag$.

#### 3.5.2 Simulation Two: $3.6 \leq L_{AC} < 4$

Fig 7 shows that memory format for $Ag$ is chaotic with $L_{AC} = 3.8$. As for the memory format of mutated antigen $Ag'$, Fig. 8 illustrates a better view that two memory formats are completely different. In this case, the corresponding $AC$ cannot activate a cross-reactive immune response to $Ag'$; $Ab_1$ cannot effectively eliminate $Ag'$ clones.

For $L_{AC} = 3.8$, the unstable fixed point of (4) is equal to 0.7368. By calculating $p = f(q)$ and $q = f(p)$, where
For mutated antigens. Our model focuses on the memory forming process which is unique while comparing to other researches. For example, Anderson et al. studied intensively about the immune network model with antibody dynamics based on Cayley tree [16]. Our model also proposes a way of controlling non-associative memory forming based on the OGY method.

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